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Posted Date: 9 January 2025

doi: 10.20944/preprints202501.0658.v1

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Article

A Cross-Sectional Survey of Oral Adverse Events and Oral Management Needs in Outpatients Receiving Cancer Drug Therapy

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Simple Summary: Oral adverse events during cancer drug therapy cause severe pain, difficulty eating, loss of taste, and impaired speech; they may also affect patient quality of life. We investigated the incidence and severity of oral adverse events in outpatients receiving cancer drug therapy and the necessity for intervention by dental professionals. The results of our questionnaire-based survey suggest that oral adverse events negatively affect the daily lives of outpatients receiving cancer drug therapy. More than a quarter of outpatients receiving cancer drug therapy indicated the need for oral management through dental interventions. Patients receiving 5FU-, taxane-, and anthracycline-based regimens, in particular, may require oral management by dental professionals.

Abstract: Objectives: The aim of this study was to investigate the incidence and severity of oral adverse events in outpatients receiving cancer drug therapy and the need for intervention by dental professionals. **Methods:** A questionnaire-based survey was conducted among patients who received cancer drug therapy at our hospital between September 1 and 30, 2022. The incidence and severity of oral adverse events and the need for intervention by dental professionals were investigated. The risk factors for these events were also analyzed. **Results:** Of the 216 patients who answered the questionnaire, 127 (58.8%) experienced oral adverse events such as dysgeusia, oral mucositis, and xerostomia. Of the patients who experienced oral adverse events, 53.5% showed that they wanted to improve their condition, 34.6% showed that the adverse events caused problems in their daily lives, and 26.8% wanted dental intervention. Thirty-two patients (25.2%) reported that the symptoms of these oral events were as severe as or more severe than those of other adverse events. The incidence of adverse oral events was significantly higher in patients treated with 5FU- and taxane-based regimens than in patients treated with other regimens. **Conclusions:** Our results suggest that oral adverse events have a significant impact on outpatients receiving cancer drug therapy. More than a quarter of outpatients receiving cancer drug therapy wanted oral management through dental interventions. In particular, patients receiving 5FU-, taxane-, and anthracycline-based regimens may require oral management by dental professionals.

Keywords: outpatient; cancer drug therapy; oral adverse events; oral management

1. Introduction

Oral adverse events during cancer drug therapy not only cause severe pain, difficulty eating, loss of taste, and impaired speech but may also affect the daily lives of patients [1]. Several scientific societies have developed guidelines for the oral management of patients receiving cancer treatment [1–4]. The Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) emphasize the importance of appropriate oral management by multidisciplinary medical teams involving well-trained dentists or dental hygienists to prevent and treat oral adverse events [3,4]. Oral management is generally performed by multidisciplinary teams

 doi:10.20944/preprints202501.0658.v1

in patients receiving bone marrow transplantation and head and neck radiotherapy because the incidence of oral adverse events observed during these treatments is high [5–7]. However, outpatients receiving cancer drug therapy do not undergo oral management because the incidence of oral adverse events is considered low [1]. Therefore, outpatients receiving cancer drug therapy may not receive appropriate oral management. However, outpatients receiving cancer drug therapy may be at a higher risk of adverse oral events than expected because high-intensity treatments are increasingly being administered on an outpatient basis [8,9].

The aim of this study was to clarify the frequency and severity of oral adverse events in outpatients receiving cancer drug therapy and to clarify patient needs for the management of oral adverse events by medical professionals.

2. Materials and Methods

2.1. Patients

This cross-sectional survey was conducted at the Outpatient Cancer Chemotherapy Center of Niigata University Medical and Dental Hospital from September 1st to 30th, 2022. Patients 1) with cancer, 2) who were receiving cancer drug therapy at the Outpatient Cancer Chemotherapy Center, and 3) who were over 18 years of age, were eligible for inclusion. Patients 1) who did not agree to participate in the study, 2) who were receiving or had received radiation therapy, and 3) who were receiving oral care from dental professionals such as dentists or dental hygienists, were excluded. This study was approved by the Ethics Committee of the Niigata University School of Medicine (approval number: 2022-0120).

2.2. Data Collection and Survey

This survey was conducted using a questionnaire designed with reference to the Patient-Reported Outcome (PRO) Common Terminology Criteria for Adverse Events (PRO-CTCAE) (Table 1) [10,11]. Data on the incidence and severity of oral adverse events, the need for oral adverse event management by dental professionals, and the impact of these events on daily life were collected and evaluated.

Table 1. Items on the patient evaluation questionnaire used in this study.

Q 1.	What type of oral adverse events do you have?
	1. Mucositis. 2. Tongue coating. 3. Dysgeusia. 4. Xerostomia. 5. Stickiness of saliva. 6. Numbness around the mouth 7. Oral pain 8. Oral discomfort. 8. None.
Q 2.	Do you want to improve the oral adverse events?
	1. Yes. 2. No.
Q 3.	Do the oral symptoms cause problems in your daily life?
	1. Yes. 2. No.
Q 4.	What issues have become a problem in your daily life?
	1. Reduced food intake. 2. Increased food intake. 3. Drinking too much. 4. Drinking not much. 5. Difficulty swallowing. 6. Sleeplessness. 7. Impaired speech. 8. None.
Q 5.	Do you want medication or a treatment method for oral adverse events?
	1. Yes. 2. No.
Q 6.	Do you want dentist intervention to improve your oral adverse events?
	1. Yes. 2. No
Q 7.	How severe are the oral adverse events compared with non-oral adverse events?
	1. More severe. 2. similar. 3. Not as severe.

2.3. Statistical Analysis

The sample size was not set because this was a cross-sectional study. The relationship between patient characteristics and major oral adverse events was analyzed using EZR ver.1.66 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [12], which is a graphical user interface for

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R (The R Foundation for Statistical Computing, Vienna, Austria). It is a modified version of the R commander designed to add statistical functions frequently used in biostatistics. Uni- and multivariate logistic regression analyses were used to identify the predictors of major oral adverse events. $P<0.05$ was considered statistically significant.

3. Results

Two hundred and sixteen patients were enrolled in this study. The patient characteristics are shown in Table 2.

Table 2. Patient characteristics (n = 216).

	Patient characteristics	n	%
Sex	Male	108	50.0%
	Female	108	50.0%
Age group (years old)	AYA (18–39)	8	3.7%
	Middle aged (40–69)	122	56.5%
	Old aged (≥70)	86	39.8%
Cancer type	Breast cancer	52	24.1%
	Lung cancer	45	20.8%
	Gastrointestinal cancer	37	17.1%
	Liver, biliary tract, pancreatic cancer	18	8.3%
	Urological cancer	17	7.9%
	Gynecological cancer	14	6.5%
	Hematological cancer	12	5.6%
	Head and neck cancer	7	3.2%
	Soft tissue sarcoma	3	1.4%
	Others	11	5.1%
Cancer drug therapy	ICIs（Atezolizumab, Durvalumab, Pembrolizumab, Nivolumab, Avelumab）	67	31.0%
	Taxane-based (DTX, PTX, nab-PTX, CBZ)	49	22.7%
	5FU-based (5FU, TS-1, Cape)	33	15.3%
	Anthracycline-based	8	3.7%
	CDDP-based	4	1.9%
	EGFR antibodies (Cet, Pani)	3	1.4%
	Others	52	24.1%

AYA, Adolescent and young adult; ICIs, Immune checkpoint inhibitors; DTX, Docetaxel; PTX, Paclitaxel; nab-PTX, nab-Paclitaxel; CBZ, Cabazitaxel acetonate; Cape, Capecitabine; CDDP, Cisplatin; EGFR, Epidermal growth factor receptor; Cet, Cetuximab; Pani, Panitumumab

More than half of the patients were middle-aged (aged 40–69 years). The major cancer types were breast, lung, and gastrointestinal cancers. Patients had received the following cancer drug therapies: immune checkpoint inhibitors (ICIs), taxane-based regimens, 5-fluorouracil-based regimens (5-FU), anthracycline-based regimens, cisplatin (CDDP)-based regimens, and monoclonal antibody drugs targeting epidermal growth factor receptor (EGFR). The most commonly used drug therapies were ICIs, and taxane- and 5FU-based regimens (31.0, 22.7, and 15.3%, respectively).

3.1. Incidence of Oral Adverse Events

One hundred and twenty-seven patients (58.8%) experienced adverse oral events (Table 3-1). These included dysgeusia, oral mucositis, xerostomia, tongue coating, stickiness, oral discomfort, oral pain, and numbness around the mouth (Figure 1). The most prevalent oral adverse events were dysgeusia, oral mucositis, and xerostomia, with incidence rates of 25.9, 21.3, and 19.4%, respectively (Table 3-2).

 doi:10.20944/preprints202501.0658.v1

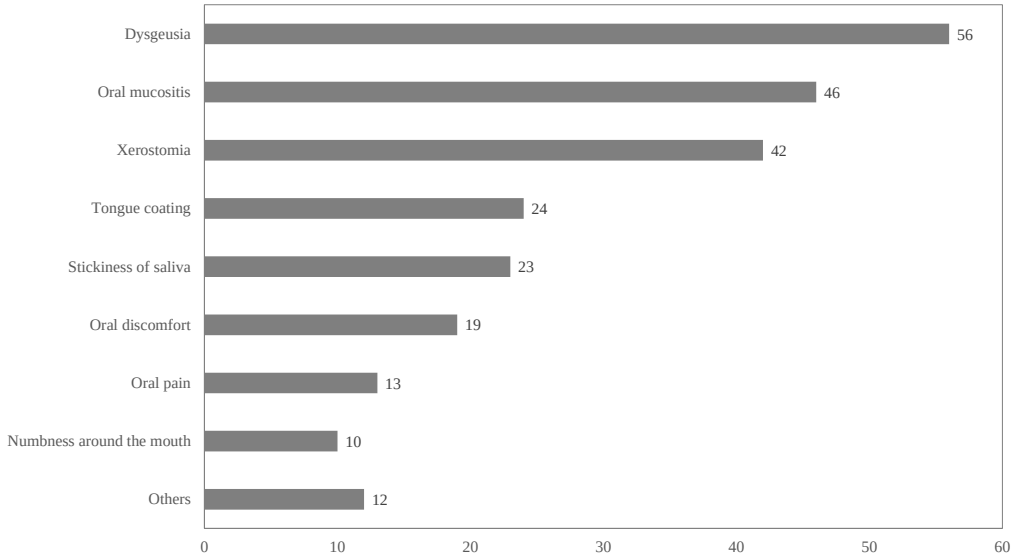

Figure 1. Details of the adverse events. This figure shows the number of patients with oral adverse events, as determined using the questionnaire. The survey allowed for multiple answers.

Table 3. The relationship between patient characteristics and oral adverse events.

			With	Without	Multivariate analysis		
		n	n(%)	n(%)	OR	95%CI	*P-value*
		216	127(58.8)	89(41.2)			
Sex	Male	109	54(49.5)	55(50.5)			
	Female	107	73(68.2)	34(31.8)	1.14	0.48-2.70	0.76
Age group (years)	AYA (18–39)	8	4(50.0)	4(50.0)			
	Middle-aged (40–69)	122	77(63.1)	45(36.9)	3.21	0.59-17.70	0.18
	Older (≥ 70)	86	46(53.5)	40(46.5)	2.7	0.45-16.10	0.28
Cancer type	Others	11	4(36.4)	7(63.6)			
	Breast cancer	51	38(74.5)	13(25.5)	6.38	1.05-38.90	0.04*
	Lung cancer	46	18(39.1)	28(60.9)	1.45	0.31-6.73	0.64
	Gastrointestinal cancer	37	27(73.0)	10(27.0)	2.79	0.42-18.40	0.29
	Liver, biliary tract, pancreatic cancer	18	12(66.7)	6(33.3)	1.42	0.21-9.70	0.72
	Urological cancer	17	6(35.3)	11(64.7)	1.29	0.22-7.62	0.78
	Gynecological cancer	14	9(64.3)	5(35.7)	6	0.82-43.90	0.08
	Hematological cancer	12	7(58.3)	5(41.7)	5.61	0.76-41.70	0.09
	Head and neck cancer	7	5(71.4)	2(28.6)	5.25	0.57-48.10	0.14
	Soft tissue sarcoma	3	1(33.3)	2(66.7)	0.9	0.05-17.30	0.95
Cancer drug therapy	Others	51	26(51.0)	25(49.0)			
	5FU-based (5FU, S1, Cape)	33	27(81.8)	6(18.2)	9.37	1.74-50.40	< 0.01*
	Taxanes-based (DTX, PTX, nab-PTX, CBZ)	49	37(75.5)	12(24.5)	5.63	1.91-16.60	< 0.01*
	Anthracyclines-based	8	6(75.0)	2(25.0)	1.95	0.35-10.90	0.45
	ICIs (Atezolizumab,Durvalumab,Pembrolizumab,Nivolumab,Avelumab)	68	27(39.7)	41(60.3)	1.69	0.55-5.19	0.36
	EGFR antibodies (Cet, Pani)	3	1(33.3)	2(66.7)	0.84	0.05-14.50	0.91
	CDDP	4	3(75.0)	1(25.0)	11.1	0.80-156.00	0.07

†Significant association (*p-value* < 0.05)
OR:odds ratio
CI:confidence interval

 doi:10.20944/preprints202501.0658.v1

Table 3. The relationship between cancer drug therapies and major oral adverse events.

			With	Without	Multivariate analysis		
		n	n(%)	n(%)	OR	95%CI	*P-value*
Dysgeusia		216	56(25.9)	160(74.1)			
	Others	51	9(17.6)	42(82.4)			
	5FU-based (5FU, S1, Cape)	33	12(36.4)	21(63.6)	1.36	0.23-8.19	0.74
	Taxanes-based (DTX, PTX, nab-PTX, CBZ)	49	22(44.9)	27(55.1)	4.76	1.61-14.10	< 0.01*
	Anthracyclines-based	8	4(50.0)	4(50.0)	3.50	0.71-17.30	0.13
	ICIs（Atezolizumab,Durvalumab,Pembrolizumab, Nivolumab,Avelumab）	68	7(10.3)	61(89.7)	0.74	0.19-2.89	0.66
	EGFR antibodies (Cet, Pani)	3	1(33.3)	2(66.7)	1.19	0.06-24.60	0.91
	CDDP	4	1(25.0)	3(75.0)	3.15	0.21-47.90	0.41
Oral mucositis		216	46(21.3)	170(78.7)			
	Others	51	13(25.5)	38(74.5)			
	5FU-based (5FU, S1, Cape)	33	13(39.4)	20(60.6)	2.70E+00	0.44-16.50	0.28
	Taxanes-based (DTX, PTX, nab-PTX, CBZ)	49	14(28.6)	35(71.4)	1.85E+00	0.65-5.25	0.25
	Anthracyclines-based	8	2(25.0)	6(75.0)	7.38E-01	0.13-4.21	0.73
	ICIs（Atezolizumab,Durvalumab,Pembrolizumab, Nivolumab,Avelumab）	68	4(5.9)	64(94.1)	4.48E-01	0.10-2.00	0.29
	EGFR antibodies (Cet, Pani)	3	0(0.0)	3(100.0)	7.68E-08	0-Inf	0.99
	CDDP	4	0(0.0)	4(100.0)	1.50E-07	0-Inf	0.99
Xerostomia		216	42(19.4)	174(80.6)			
	Others	51	6(11.8)	45(88.2)			
	5FU-based (5FU, S1, Cape)	33	11(33.3)	22(66.7)	1.65E+01	1.74-157.00	0.01*
	Taxanes-based (DTX, PTX, nab-PTX, CBZ)	49	11(22.4)	38(77.6)	2.65E+00	0.80-8.79	0.11
	Anthracyclines-based	8	2(25.0)	6(75.0)	2.05E+00	0.32-13.10	0.45
	ICIs（Atezolizumab,Durvalumab,Pembrolizumab, Nivolumab,Avelumab）	68	11(16.2)	57(83.8)	2.29E+00	0.55-9.53	0.25
	EGFR antibodies (Cet, Pani)	3	0(0.0)	3(100.0)	8.49E-07	0-Inf	1.00
	CDDP	4	1(25.0)	3(75.0)	7.63E+00	0.39-148.00	0.18

†Significant association (*p-value* < 0.05)
OR:odds ratio
CI:confidence interval

 doi:10.20944/preprints202501.0658.v1

3.2. Patient Needs for Management of Oral Adverse Events by Medical Professionals

Sixty-eight patients (53.5%) wanted improvement of their oral adverse events. Furthermore, 44 patients (34.6%) had oral adverse events that affected their daily lives, and 34 patients (26.8%) wanted professional oral care from well-trained dentists and dental hygienists. Thirty-two patients (25.2%) experienced oral adverse events that were as severe or even more severe than other adverse events (Table 4).

Table 4. Responses to the question: Do you require management of oral adverse events by medical professionals?

		Response		
	Total	**Yes**		**No**
Item	n(%)	n(%)		n(%)
Hope for improvement of oral adverse events	115(90.6)	68(53.5)		47(37.0)
Impact on their daily lives	113(89.0)	44(34.6)		69(54.3)
Hope for professional oral care (Well-Trained Dentist and Dental Hygienist)	102(80.3)	34(26.8)		68(53.5)
		more severe	similar	not as severe
Comparison of the severity of oral adverse events and other adverse events	113(89.0)	5(3.9)	27(21.3)	81(63.8)

3.3. The Relationship Between Patient Characteristics and Major Oral Adverse Events

The relationship between oral adverse events and patient characteristics is shown in Table 3-1. Dysgeusia, oral mucositis, and xerostomia were the major oral symptoms (Table 3-2).

Patients with breast cancer experienced significantly more oral adverse events than other patients (OR=6.38; 95%CI=1.05–38.90; P=0.04). Patients receiving 5FU- and taxane-based regimens had significantly more oral adverse events than those receiving other regimens (OR=9.37; 95%CI=1.74–50.40; P<0.01 and OR=5.63; 95%CI=1.91–16.60; P<0.01, respectively). The incidence of oral mucositis did not differ significantly between any of the regimens. Dysgeusia was significantly higher in taxane-based regimens than in the other regimens (OR=4.76; 95%CI=1.61–14.10; P<0.01). The incidence of xerostomia was significantly higher in 5FU-based regimens than in the other regimens (OR=16.5; 95%CI=1.74–157.00; P=0.01).

4. Discussion

The objective of this study was to clarify the frequency and severity of oral adverse events in outpatients receiving cancer drug therapy and to clarify patients' needs for oral adverse event management by dental professionals. Our findings have several important clinical implications. First, more than half of the outpatients receiving cancer drug therapy had oral adverse events. Second, more than a quarter of the patients who experienced oral adverse events felt that these symptoms were as severe or even more severe than other non-oral adverse events. Third, more than a quarter of the patients who experienced oral adverse events wanted oral management through professional intervention by well-trained dentists and dental hygienists. These results indicate that oral adverse events have a significant negative impact on patients receiving outpatient cancer drug therapy.

The guidelines for supportive care in cancer have described the importance of interventions by multidisciplinary medical teams involving well-trained dentists and dental hygienists to manage oral adverse events [3,4,13]. The guidelines indicate that professional dental intervention is essential for patients at high risk of oral adverse events, such as those undergoing bone marrow transplantation and head and neck radiotherapy. Conversely, outpatient chemotherapy is currently associated with a low risk of adverse oral events. However, our results suggest that adverse oral events also have a significant impact on outpatients receiving cancer drug therapies, highlighting their need for oral management by dental professionals.

 doi:10.20944/preprints202501.0658.v1

Our results showed that taxane-based regimens had the highest incidence of dysgeusia. Taxane-based drug therapies affect neurosensory perception [14]. Therefore, the cause of the dysgeusia was considered to be neuropathy due to taxane-based drug therapies. Prolonged dysgeusia not only worsens nutritional and performance status but may also make it difficult to continue cancer therapy [15–18]. Therefore, outpatients receiving taxane-based regimens should be aware of the risk of developing dysgeusia due to neuropathy.

According to the 2020 edition of the guidelines for managing mucositis during cancer drug therapy, anticancer drugs such as anthracycline-based, 5FU-based, and methotrexate regimens are associated with a higher incidence of oral mucositis [1]. Our results showed no significant differences in the incidence of oral mucositis among the cancer drug therapies. However, the incidence of oral mucositis was >25% for all regimens, excluding ICIs. Oral mucositis increases the risk of systemic complications, such as malnutrition, cachexia, and systemic infections [19,20]. Furthermore, oral mucositis negatively affects treatment outcomes and medical costs [21]. Therefore, the incidence of oral mucositis should be considered even in outpatient settings.

Our study showed the highest incidence of xerostomia when 5FU-based regimens were used. A previous study reported that patients receiving cyclophosphamide, epirubicin, methotrexate and 5FU experienced a higher incidence of xerostomia [22]. 5FU-based regimens are widely used to treat many solid tumors. They are also used in outpatient chemotherapy. Xerostomia can cause oral discomfort and functional impairment [23]. It results in a reduction in the physiological effects of saliva, including antibacterial activity, mucosal protection, and assistance with taste. Therefore, xerostomia may exacerbate dysgeusia and oral mucositis [24–26].

Our results showed that more than a quarter of the patients who experienced oral adverse events wanted oral interventions by dental professionals. These results show that outpatients receiving cancer drug therapy also require appropriate oral management by a multidisciplinary medical team. However, the number of outpatients receiving cancer drug therapy is very high. Therefore, an efficient patient selection system would be essential [27].

Our study has several limitations. First, the results were based on subjective patient-reported questionnaire surveys and did not reflect evaluations by medical professionals. Discrepancies may occur between patient and medical professional evaluations [28–30]. Thus, patient and medical professional assessments should be considered in future studies. Second, because the survey in this study was based on patient-reported questionnaires, the communication abilities of the patients and the absence of opinions from non-responders may have influenced the results. Third, although drug therapies containing anthracyclines or anti-EGFR antibodies are associated with a higher incidence of oral mucositis, only a limited number of patients were included in this study. Thus, assessment of the necessity for professional medical intervention in outpatients treated with these drug therapies was difficult. We performed multivariate analysis to reduce these biases. Fourth, because the survey was conducted at a single hospital, there was a potential bias in patient background and cancer drug therapy, leading to possible discrepancies. We plan to focus on 5FU-, taxane-, and anthracycline-based regimens and use more established adverse event assessment methods, such as PRO-CTCAE, for validation in future studies. Finally, our study had a cross-sectional design; therefore, the sample size was small. However, to maximize the number of participants, we requested consent from all eligible individuals.

5. Conclusions

Our results suggest that oral adverse events negatively affect the daily lives of outpatients receiving cancer drug therapy. More than a quarter of outpatients receiving cancer drug therapy wanted oral management through dental interventions. In particular, patients receiving 5FU-, taxane-, and anthracycline-based regimens may require oral management by dental professionals.

Future studies should introduce evaluation methods based on PRO-CTCAE and CTCAE and collect data from a diverse patient population through multicenter collaborative studies. Furthermore, the adoption of a longitudinal study design will facilitate investigation of the time

 doi:10.20944/preprints202501.0658.v1

course of oral adverse events and the impact of appropriate oral care on quality of life and treatment continuity. This is expected to lead to more effective and practical interventions and improved quality of care.

Author Contributions: Conceptualization Y.S. and K.K.; Data Collection Y.S. and M.K.; Formal analysis and investigation, Y.S.; Writing original draft preparation: Y.S., K.K., A.T. All authors critically revised the article and approved the final version for publication.

Funding: This research received no external funding.

Institutional Review Board Statement: The survey was conducted among patients who provided voluntary consent. This study was conducted in compliance with the "Ethical Guidelines for Medical Research Involving Human Subjects" and was approved by the Ethics Committee of Niigata University School of Medicine (approval number: 2022-0120). The purpose of the research was posted to the Outpatient Cancer Drug Therapy Center and confidentiality was ensured. Informed consent was obtained from all participants after they returned the completed questionnaire.

Informed Consent Statement: Not applicable.

Data Availability Statement: The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Acknowledgments: We would like to thank Editage (www.editage.jp) for the English language editing.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

MASCC	Multinational association of supportive care in cancer
ISOO	International society of oral oncology
PRO-CTCAE	Patient-Reported Outcome Common Terminology Criteria for Adverse Events
5-FU	5-fluorouracil
ICIs	Immune checkpoint inhibitors
CDDP	Cisplatin
EGFR	Epidermal growth factor receptor

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